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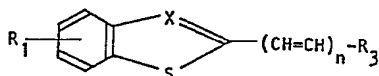
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(54) **Benzothiazole and benzothiophene derivatives.**

(57) The invention relates to compounds of the general formula I



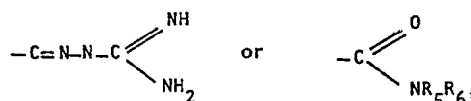
wherein

R₁ represents one up to and including four, the same or different substituents selected from alkyl (1-6 C), alkoxy (1-6 C), hydroxy, halogen, NO₂, CF₃ or the group -NR₅R₆, whereby two substituents taken together may also represent a methylene-dioxy group,
X represents nitrogen or the group



n has the value 0, 1 or 2,

R₃ represents one of the moieties:



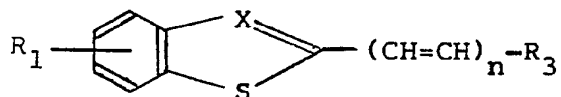
the latter meaning of R₃ (amide) only under the condition that for X is nitrogen the meaning of R₁ is limited to substituents selected from hydroxy, alkoxy (1-6 C) and methylenedioxy, and R₄, R₅ and R₆ represent hydrogen or alkyl (1-6 C), and pharmaceutically acceptable salts thereof, suitable in the treatment of heart failure.

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BENZOTHIAZOLE AND BENZOTHIOPHENE DERIVATIVES.

The invention relates to compounds of the general formula I

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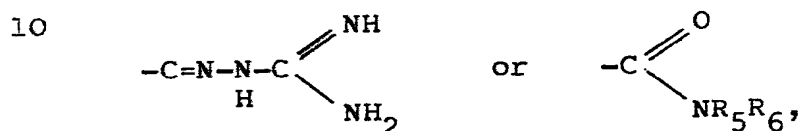
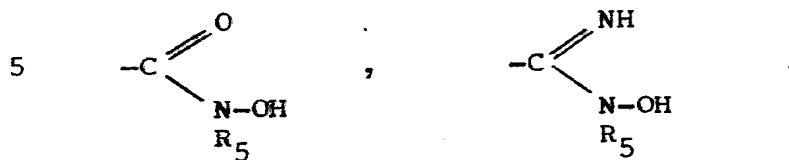
wherein

10 R_1 represents one up to and including four, the same or different substituents selected from alkyl(1-6 C), alkoxy(1-6 C), hydroxy, halogen, NO_2 , CF_3 or the group $-\text{NR}_5\text{R}_6$, whereby two substituents taken together may also represent a methylene-dioxy group,

15

X represents nitrogen or the group $-\overset{\text{R}_4}{\underset{|}{\text{C}}} =$,
 n has the value 0, 1 or 2,

R_3 represents one of the moieties:

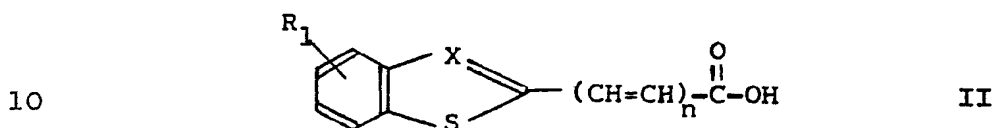


15 the latter meaning of R_3 (amide) only under the condition that for X is nitrogen the meaning of R_1 is limited to substituents selected from hydroxy, alkoxy(1-6 C) and methylenedioxy, and R_4 , R_5 and R_6 represent hydrogen or alkyl(1-6 C)
20 and pharmaceutically acceptable salts thereof.

25 The compounds according to the invention have a cardiotonic activity and more particularly they show a very potent increase of the force and energy of the heart-muscular contractions (positive inotropic effect).

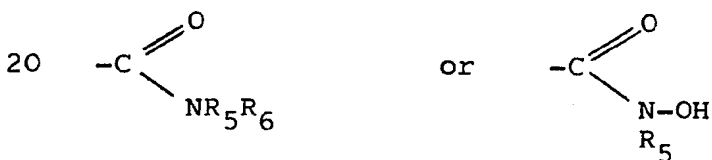
The compounds of the invention may be prepared by any method known for the preparation of analogous compounds.

A very suitable starting product for the preparation of the compounds I is a compound of the formula II

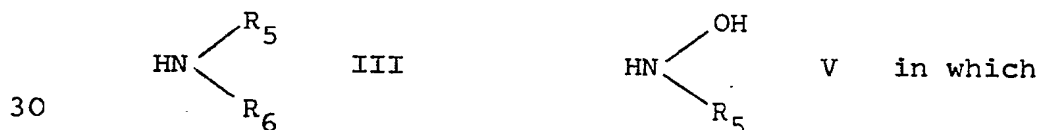


wherein R_1 , n and X have the aforesaid meanings.

15 Compounds of the invention in which R_3 represents the moiety

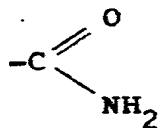


may for example be prepared by reacting the compound of formula II or an acid halide or anhydride thereof with an amine of the formula III or hydroxylamine of the formula V:



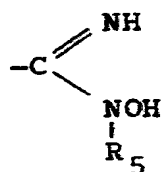
R_5 and R_6 have the aforesaid meaning, or a reactive derivative thereof, in which the hydrogen atom is replaced by a more reactive moiety, such as an alkali metal.

Compounds of formula I, in which R_3 represents the moiety



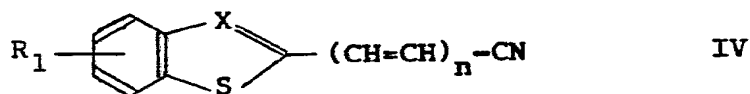
may also be prepared by reacting a compound of formula II or an acid halide or anhydride thereof with an alkali metal azide, followed by reduction of the resulting azide.

Compounds of the invention in which R_3 represents a



moiety may, for example,

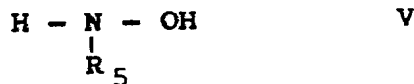
be prepared from a nitrile of the general formula IV:



in which R_1 , X and n have the meanings

assigned before

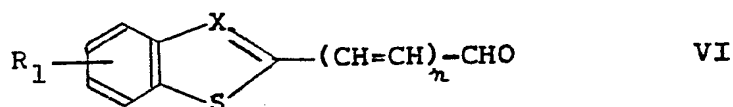
by reacting the said nitrile in the usual manner with a compound of the formula V:



wherein R_5 has the aforesaid meanings, or a reactive derivative thereof, in which hydrogen (at the nitrogen atom) has been replaced by a more reactive moiety, such as an alkali metal.

The nitrile of formula IV may be prepared in the usual manner from the corresponding carboxylic acid of formula II by converting the carboxylic acid into the corresponding carboxamide followed by dehydration of the carboxamide.

Compounds of the invention, in which R_3 represents a $-C=N-NH-C(=NH)NH_2$ moiety, may most conveniently be prepared from an aldehyde of the formula:



by condensation of this compound (VI) with amino guanidine or a salt thereof.

The aldehyde of formula VI can be prepared in various manners. For example the aldehyde may be manufactured by reducing the carboxylic acid of formula II in a well known manner.

Another convenient synthesis for preparing the aldehyde consists of a mild reduction of the corresponding nitrile of formula II, e.g. with the aid of a metal hydride such as diisobutylaluminiumhydride.

The starting product of general formula II may be prepared by known methods. The attached flow sheet shows the preparation of a compound of formula II, wherein $n = 0$. Chain length extension to $n = 1$ and $n = 2$ can be obtained by converting the carboxylic acid II ($n = 0$) into the corres-

ponding aldehyde ($n = 0$) and reacting said aldehyde with the appropriate phosphonate-ylid using reaction conditions well known in carrying out the Wittig reaction.

5 Appropriate phosphonate ylids are, for example, cyanomethylene triphenylphosphorane, carboxymethylene triphenylphosphorane and corresponding (alkyl)esters, and 3-cyano propen(2)-ylidene triphenylphosphorane. If necessary, the
10 nitrile - obtained through this Wittig reaction - can be converted into the corresponding amide or carboxylic acid.

15 Preferably most substituents at the benzo- ring (see R_1) are already present in one of the starting products. Nevertheless it is very well possible to convert a substituent R_1 into another substituent R_1 after the above mentioned condensation reactions.

20 Thus, one or more hydroxy groups (R_1) may be converted into the corresponding alkoxy groups or halogen in the usual manner. Furthermore two hydroxy groups may be converted into one methylene-dioxy group and an alkoxy group may
25 be hydrolysed to the corresponding hydroxy group.

30 The compounds according to the general formula I may be converted into a pharmaceutically acceptable salt.

35 The compounds of formula I which have an alkaline character may be obtained as the free base or as an acid addition salt. If required, however, the free base I can be prepared from the salt, for example by reaction with an alkaline

compound or by means of an ion exchanger, whilst the free base I can be converted in a simple manner into an acid addition salt.

5 Pharmaceutically acceptable acid addition salts are derived from acids, such as hydrochloric acid, sulphuric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, maleic acid, fumaric acid, malonic acid, succinic acid,
10 tartaric acid, lactic acid, citric acid, ascorbic acid, salicylic acid, benzoic acid and methane - sulphonc acid.

 Compounds I having an acidic nature may be converted into a metal salt, preferably an
15 alkali metal salt such as the sodium salt.

 By the term "alkyl(1-6 C)" as used in the definitions of R_1 , R_4 , R_5 and R_6 is meant a saturated hydrocarbon with 1 to 6 carbon atoms,
20 and preferably 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert. butyl, pentyl and isopentyl.

 An alkoxy(1-6 C) group is an alkyloxy group, in which the term alkyl has a similar
25 meaning as above.

 By halogen in the definition of R_1 is preferably meant iodine, bromine, chlorine and fluorine. The most preferred halogens are chlorine and bromine.

30 The said compounds in accordance with the invention can be administered either orally, locally or parenterally, preferably in a daily dose between 0.01 and 50 mg/kg body weight. For this purpose the compounds are processed in a
35 form suitable for oral, local or parenteral

administration, for example a tablet, pill, capsule, solution, suspension, emulsion, paste or spray. The oral form is the most preferred form of administration.

5

The most potent inotropic compounds are found amongst those compounds of formula I in which at least two substituents R_1 are present selected from hydroxy or alkoxy or in which at least one methylene-dioxy group (R_1) is present, whereby the dimethoxy or methoxy-hydroxy substitution pattern is most preferred.

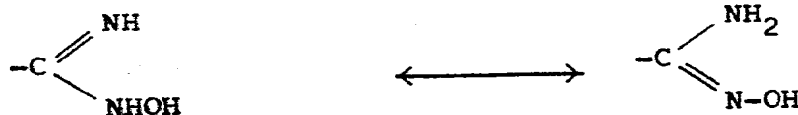
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Preferred compounds of formula I are moreover those compounds I in which X is $-\text{CH}=\text{}$.

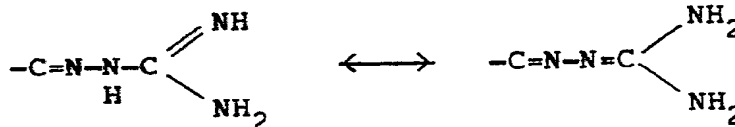
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The position of the double bond between nitrogen and carbon in some of the moieties defined by R_3 of formula I cannot be clearly specified, because an equilibrium will prevail between:

20



25



30

The preferred R_3 moiety in the compounds of the invention is the amide moiety and especially the N-hydroxy-(carbox)imidamide moiety.

35

The preferred value of n is 0 or 1.

Example 15,6-Dimethoxy-benzo[b]thiophene-2-carboxamide.

A mixture of 5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid (68.8 g), dry toluene (350 ml),
5 thionyl chloride (126 ml) and pyridine (1.75 ml) was stirred and heated at reflux for 4 hours. The resultant mixture was cooled, evaporated to dryness under vacuum and the residue was purged with dry toluene (3 x 250 ml). The resulting crude acid
10 chloride was suspended in dioxan (160 ml) then cooled in an ice bath and treated in one portion with concentrated ammonium hydroxide solution (33% w/w, 900 ml). This gave a suspension of brown solid which was stirred for two hours then
15 filtered, washed with water and dried under vacuum over calcium chloride at 60 °C to give 5,6-dimethoxy-benzo[b]thiophene-2-carboxamide (62.5 g), m.p. 211-213 °C.

20

Example 2A. 5,6-Dimethoxy-benzo[b]thiophene-2-carbonitrile.

5,6-Dimethoxy-benzo[b]thiophene-2-carboxamide (65 g) was suspended in pyridine (325 ml). The solution was cooled to 0 °C and treated dropwise
25 with trifluoro acetic anhydride (185 ml) whilst maintaining the internal reaction temperature below 10 °C. The mixture was then stirred at room temperature for 30 min. then cooled and treated dropwise with water (170 ml) whilst maintaining
30 the internal temperature below 30 °C. The reaction mixture was diluted with more water (800 ml), stirred and the brown solid was filtered and dried under vacuum over calcium chloride at 60 °C. Recrystallisation from acetone/ether afforded
35 5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile

as a white solid (47 g), m.p. 125 °C.

B. N-Hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide

5 Sodium metal (1.86 g) was cut into small pieces and added to a stirred methanol solution (30 ml) under an atmosphere of nitrogen. When all the sodium had dissolved the hot solution was treated with a warm solution of hydroxylamine
10 hydrochloride (5.65 g) in methanol (40 ml). After 1 h. the white suspension of sodium chloride was filtered off and the filtrate was added to 5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile (6.0 g). The solution was stirred at 50 °C for
15 3 hours then cooled, diluted with water (400 ml), stirred and the white solid filtered and dried to give N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide (6.74 g), m.p. 216-219 °C (decomp.).

20 The free base was dissolved in methanol (120 ml), stirred, and the solution was saturated with hydrogen chloride gas. After 5 min. the solution was concentrated, diluted with ether and the white solid was filtered. Recrystallisation
25 from methanol:ether (1:2) afforded pure N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide hydrochloride (6.8 g), m.p. 203-210 °C. Melting point mesylate salt: 211-212 °C.

Example 3

30 A. 5,6-Dihydroxy-benzo[b]thiophene-2-carbonitrile.

5,6-Dimethoxy-benzo[b]thiophene-2-carbonitrile (9.0 g) was dissolved in dichloromethane (135 ml) and the solution was stirred and cooled to -70 °C and treated at a rapid dropwise
35 rate with a cold solution of boron tribromide

(19.5 ml) in dichloromethane (60 ml). The resultant suspension was stirred at room temperature for 1 h. then poured into ice-cold water (1000 ml). The light coloured solid was filtered, dried, dissolved
5 in acetone:hexane (1:1) then eluted through coarse silica (0.2-0.5 mm, Merck, 50 g) in acetone:hexane (1:1). The appropriate fractions were combined, evaporated to dryness and crystallised from acetone/n-hexane to give 5,6-dihydroxy-benzo[b]
10 thiophene-2-carbonitrile (7.5 g), m.p. 229-230 °C.

B. N-5,6-Trihydroxy-benzo[b]thiophene-2-carboximidamide hydrochloride.

Using the procedure described in Example 2B,
15 5,6-dihydroxy-benzo[b]thiophene-2-carbonitrile was converted into N-5,6-trihydroxy-benzo[b]thiophene-2-carboximidamide hydrochloride.

Free base, m.p. 188-190 °C (decomp.).

Hydrochloride, m.p. 200-205 °C (decomp.).

20

Example 4

A. Thieno[2,3-f]-1,3-benzodioxole-6-carbonitrile.

A mixture of powdered potassium hydroxide (12.36 g) and dimethylsulphoxide (100 ml) was
25 stirred at room temperature for 5 min. then treated with 5,6-dihydroxy-benzo[b]thiophene-2-carbonitrile (5.26 g). After 1 minute di-iodomethane (4.4 ml) was added and the suspension was stirred at room temperature for 75 minutes, then more di-iodomethane
30 (2.2 ml) was added. After a further 30 minutes the reaction was poured into water (500 ml) and extracted with ethyl acetate (2 x 100 ml). The organic extracts were combined, washed with 2M HCl and saturated brine, then dried and evaporated
35 to give a brown crystalline residue. The crude

product was suspended in hot dichloromethane (200 ml), filtered, and the filtrate was passed through a column of silica gel (0.2-0.5 mm, Merck, 25 g). The appropriate fractions were combined and evaporated to dryness to give a white solid (3.4 g). Crystallisation from acetone/ether afforded pure thieno[2,3-f]-1,3-benzodioxole-6-carbonitrile, m.p. 179-180 °C.

10 B. N-Hydroxy-thieno[2,3-f]-1,3-benzodioxole-6-carboximidamide hydrochloride.

Using the method described in Example 2B thieno[2,3-f]-1,3-benzodioxole-6-carbonitrile was converted into N-hydroxy-thieno[2,3-f]-1,3-benzodioxole-6-carboximidamide hydrochloride.

Free base; m.p. 229-231 °C (decomp.).

Hydrochloride, m.p. 200-203 °C (decomp.).

Example 5

20 N-Hydroxy-5,6-dimethoxy-N-methyl-benzo[b]thiophene-2-carboximidamide hydrochloride.

Sodium metal (0.40 g) was cut into small pieces and added to a stirred solution of methanol (30 ml) under an atmosphere of nitrogen. When all the sodium had dissolved the solution was treated with a solution of N-methylhydroxylamine HCl (1.45 g) in methanol (30 ml). After 30 minutes the white suspension of sodium chloride was filtered off and the filtrate was added to 5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile (4.0 g). The resultant solution was stirred and heated at reflux for 5 hours then evaporated to dryness. The residue was chromatographed through a column of course silica (0.2-0.5 mm, Merck, 150 g) in dichloromethane:methanol (85:15 v/v).

The appropriate fractions were combined and evaporated to dryness to give N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide as a white solid (3.6 g). The free base was
5 dissolved in ethyl alcohol (25 ml) and dichloromethane (25 ml) then treated with a solution of dry ether (200 ml) saturated with HCl gas. The precipitated yellow solid was filtered and recrystallised from ethyl alcohol to give
10 N-hydroxy-5,6-dimethoxy-N-methyl-benzo[b]thiophene-2-carboximidamide hydrochloride (2.9 g), m.p. 237-241 °C (decomp.).

Example 6

15 A. 5,6-Dimethoxy-benzo[b]thiophene-2-carboxaldehyde.
5,6-Dimethoxy-benzo[b]thiophene-2-carbonitrile (2.0 g) was suspended in dry toluene (40 ml) under an atmosphere of nitrogen. The reaction mixture was cooled to -5 °C and treated dropwise with a
20 solution of diisobutylaluminium hydride in toluene (1.5 M, 13 ml). After 30 minutes the solution was treated with methanol (5 ml) then poured into hydrochloric acid (1M, 200 ml) and stirred for
25 15 minutes. The resultant solution was extracted into dichloromethane (4x100 ml) then the organic extracts were combined, washed with brine, dried over magnesium sulphate and evaporated to dryness. The orange residue (1.6 g) was crystallised from
30 dichloromethane:ether to give 5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde as a white solid, m.p. 155-156 °C.

B. 3-(5,6-Dimethoxy-benzo[b]thiophene-2-yl)-2-propenenitrile.

Cyanomethylene-triphenylphosphorane was prepared according to the method of S. Trippett and D.M. Walker [J.C.S., 1959, 3874-3876] and S.S. Novikov and G.A. Shvekhgeimer [C.A., 1961, 55, 13353 g].

A mixture of 5,6-dimethoxybenzo[b]thiophene-2-carboxaldehyde (8.14 g) and cyanomethylene triphenylphosphorane (22.06 g) in dry toluene (270 ml) was stirred and heated to reflux for 1 hour. The reaction mixture was then evaporated to dryness and the residue was dissolved in a mixture of dichloromethane (50 ml) and toluene (50 ml) and passed through a column of coarse silica (0.2-0.5 mm, Merck, 600 g). The column was eluted with toluene:ethyl acetate (4:1 v/v). The appropriate fractions were combined and evaporated to dryness and the residue was crystallised from dichloromethane:diethyl ether to give pure (E)-3-(5,6-dimethoxy-benzo[b]thiophene-2-yl)-2-propenenitrile (7.56 g), m.p. 154-158 °C.

C. N-Hydroxy-3-(5,6-dimethoxy-benzo[b]thiophene-2-yl)-prop-2-ene-imidamide hydrochloride.

Using the procedure described in Example 2 (E)-3-(5,6-dimethoxy-benzo[b]thiophene-2-yl)-2-propenenitrile was converted into (E)-N-hydroxy-3-(5,6-dimethoxy-benzo[b]thiophene-2-yl)-prop-2-ene-imidamide hydrochloride, m.p. 188-198 °C (decomp.).

30

Example 7

A. 4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid.

2-(3,4-Dimethoxyphenyl)-1-mercapto-acrylic acid (165.0 g) (Tetrahedron, 1969, 25, 2781-2785)

35

was dissolved in dry dioxan (800 ml) and the solution was stirred and heated at 60 °C. A solution of chlorine (87 g) in carbon tetrachloride (700 ml) was then added over 30 min.

5 After a further 45 min. the reaction mixture was concentrated under reduced pressure and the residue was triturated with acetone. The resultant pale yellow solid was filtered and dried at 65 °C to give about a 1 : 1 mixture of

10 5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid and 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid. The crude product (113 g) was suspended in ethanol (850 ml) and the mixture was stirred and treated over 5 min. with hydrogen

15 chloride gas. The resultant suspension was refluxed for 5 hours and then evaporated to dryness. The crystalline residue was purified by chromatography through silica (0.2-0.5 mm, Merck, 1.5 kg) in toluene:ethyl acetate 19:1. The

20 appropriate fractions were combined and evaporated to dryness to give 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid ethyl ester as a white solid (35 g). A portion crystallised from dichloromethane/methanol had m.p. 124-126 °C.

25

4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid ethyl ester (29.5 g) was suspended in a mixture of methanol (450 ml), water (75 ml) and potassium carbonate (20.4 g) under an

30 atmosphere of nitrogen. The reaction mixture was heated at reflux for 1 hour then cooled and poured into water (2.5 litre) containing hydrochloric acid (5M, 60 ml). The resultant white solid was filtered and dried at 65 °C under vacuum to give 4-chloro-

35 5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid .

(26.8 g). A portion crystallised from dichloromethane:methanol had, m.p. 267-270 °C.

5 B. 4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide.

Using the procedure described in Example 1, 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid was converted into 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide, m.p.
10 180-182 °C.

Example 8 •

A. 4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile.

15 Using the procedure described in Example 2A, 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide was converted into 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile, m.p.
20 159-160 °C.

B. 4-Chloro-N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide hydrochloride.

Using the procedure described in Example 2B,
25 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carbonitrile was converted into 4-chloro-N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide hydrochloride, m.p. 191-195 °C.

30 Example 9

A. 5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid ethyl ester.

5,6-Dimethoxy-benzo[b]thiophene-2-carboxylic acid (10 g) was suspended in ethanol (80 ml) and
35 the mixture was stirred and heated at reflux for

5 hours. The resultant solution was evaporated to dryness and then crystallised from dichloromethane:methanol to give 5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid ethyl ester as a white solid (9.5 g), m.p. 84-85 °C.

B. N-Hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide.

Hydroxylamine hydrochloride (5.3 g) was dissolved in warm ethanol (100 ml). The solution was stirred under an atmosphere of nitrogen and treated with a warm solution of potassium hydroxide (6.4 g) in ethanol (50 ml). After 10 min. a solution of 5,6-dimethoxy-benzo[b]thiophene-2-carboxylic acid ethyl ester (10 g) in ethanol (250 ml) was added and the resultant mixture was allowed to stand at room temperature for 72 hours. The resultant suspension was filtered to remove the precipitated potassium chloride and the filtrate was evaporated to dryness. The resultant yellow residue was dissolved in water (250 ml), filtered and the filtrate was acidified with 5M hydrochloric acid. The precipitated product was filtered and dried at 65 °C under vacuum to give N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide (8.3 g). A portion crystallised from acetone had a melting point: 179-180 °C.

C. N-Hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide sodium salt monohydrate.

N-Hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide (2.5 g) was added to a stirred solution of sodium metal (0.227 g) in methanol (55 ml). After 15 min. the solution was evaporated

to dryness and the residue crystallised from methanol:ether to give N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboxamide sodium salt monohydrate (2.7 g), m.p. 170-185 °C (decomp.).

5

Example 10

5,6-Dimethoxy-benzo[b]thiophene-2-carboxaldehyde-amino-iminomethyl hydrazone hydrochloride.

10 Aminoguanadinium hydrogen carbonate (2.5 g) was suspended in methanol (35 ml) and the mixture was treated with 5M hydrochloric acid until all the solid had dissolved. The resultant solution was added to a suspension of 5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde (4.0 g) in ethanol
15 (40 ml) and the mixture was stirred at room temperature for 16 hours under an atmosphere of nitrogen. The white suspension was then diluted with diethyl ether (250 ml) and the white solid was filtered and dried to give 5,6-dimethoxy-
20 benzo[b]thiophene-2-carboxaldehyde-amino-iminomethyl hydrazone hydrochloride (5.3 g). A portion crystallised from methanol:acetone had m.p. 271-274 °C.

25

Example 11

A. 4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde.

Using the procedure described in Example 6A, 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-
30 carbonitrile was converted into 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde, m.p. 164-165 °C.

B. 4-Chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde-amino-iminomethyl hydrazone hydrochloride.

Using the procedure described in Example 10,
 5 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde was converted into 4-chloro-5,6-dimethoxy-benzo[b]thiophene-2-carboxaldehyde-amino-iminomethyl hydrazone hydrochloride, m.p. 255-265 °C (decomp.).

10

Example 12

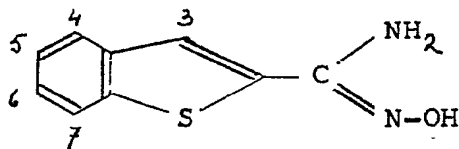
In a similar manner as described in Example 6 was prepared:

15 N-hydroxy-3-(4-chloro-5,6-dimethoxy-benzo[b]-thiophene-2-yl)prop-2-ene imidamide;
 HCl salt m.p. 192-198°C (dec),
 and mesylate salt m.p. 148-151 °C.

20 In a similar manner as described in Example 2 were prepared the following compounds all being substituted derivatives of the basic molecule:

N-hydroxy-benzo(b)thiophene-2-carboximidamide :

25



viz.

30 3-methyl-5,6-dimethoxy; HCl salt: m.p. 226-232 °C (dec.);
 5,6-dichloro; HCl salt: m.p. 199-215 °C (dec.);
 6,7-dichloro; HCl salt: m.p. 187-190 °C ;
 4,7-dichloro-5,6-dimethoxy; HCl salt: m.p. 172-196 °C (dec.);
 35 7-chloro-5,6-dimethoxy; HCl salt: m.p. 166-184 °C (dec.);

- 5-hydroxy-6-methoxy; HCl salt: m.p. 206-207 °C (dec.);
6-hydroxy-5-methoxy; HCl salt: m.p. 219-220 °C (dec.);
4-chloro-5-hydroxy-6-methoxy; HCl salt: m.p. 190 °C
(dec.);;
- 5 4,7-dimethoxy; HCl salt: m.p. 158-178 °C (dec.);
 4,5-dimethoxy; HCl salt: m.p. 173-198 °C (dec) ;
 4-chloro-5-ethoxy-6-methoxy; HCl salt: m.p.
 149-166 °C (dec.) ;
 5,7-dimethoxy; HCl salt : m.p. 190-194 °C (dec) ;
- 10 6-chloro-5,7-dimethoxy; HCl salt m.p. 212-215 °C dec ;
 5-butoxy-4-chloro-6-methoxy; HCl salt 157-166 °C dec ;
 5-ethoxy-6-methoxy; HCl salt: m.p. 208-212 °C dec ;
 4-chloro-5,6-dihydroxy; HCl salt: m.p. 230 °C dec ;
 5,6-dimethoxy-4-nitro; mesylate salt 236-237 °C dec ;
- 15 5,6-dimethoxy-7-nitro; mesylate salt 214-216 °C dec ;
 4-chloro-5,6-dimethoxy; mesylate salt 204-210°C dec ;
 4-amino-5,6-dimethoxy; HCl salt m.p. 193-195 (dec.).

Example 135,6-Dimethoxy-benzothiazole-2-carboxamide

1. A solution of potassium hydroxide (30 g) in ethanol (200 ml) was saturated with dry hydrogen sulphide. The solution was diluted with a solution of potassium hydroxide (30 g) in ethanol (200 ml) and stirred under nitrogen whilst cooled with an ice/water bath. To this was added dropwise, a solution of trichloroacetamide (37 g) in ethanol (200 ml) and the red mixture was stirred under nitrogen at room temperature for 10 minutes. To this was added a solution of chloroacetic acid (32 g) in water (200 ml) which had been first neutralised with potassium carbonate. The resulting red mixture was stirred vigorously for 10 min., allowed to stand for 30 min. and the inorganic salt was removed by filtration. The filtrate (a solution of carbamoyl-thiocarbonyl-thioacetic acid) was used without delay for further conversion.
2. The solution of carbamoyl-thiocarbonyl thioacetic acid prepared above was added to a solution of 3,4-dimethoxy-aniline (20 g) in ethanol (100 ml) and water (100 ml). The mixture was allowed to stand in a sealed vessel for 2 hr. The ethanol was evaporated under reduced pressure until crystallisation occurred. The product was collected by filtration, washed with cold ethanol, and dried to give N-(carbamoyl-thiocarbonyl)-3,4-dimethoxy-aniline (14.13 g); m.p. 149-151 °C.
3. A solution of N-(carbamoyl-thiocarbonyl)-3,4-dimethoxy-aniline (14 g) in 12% aqueous potassium hydroxide solution (1.26 l) was added slowly to a stirred solution of potassium ferricyanide (251.5 g) in water (560 ml) cooled to 10 °C. The thick, yellow precipitate formed was stirred for 30 min.,

collected by filtration, washed with water, and dried. Crystallisation from dichloromethane/ethanol gave 5,6-dimethoxy-benzothiazole-2-carboxamide (11.98 g); m.p. 211-212 °C.

5

Example 14

N-Hydroxy-5,6-dimethoxy-benzothiazole-2-carboximidamide hydrochloride.

Using the procedure described in Example 2A,
10 5,6-dimethoxy-benzothiazole-2-carboxamide was converted to 5,6-dimethoxy-benzothiazole-2-carbonitrile, m.p. 176-177 °C.

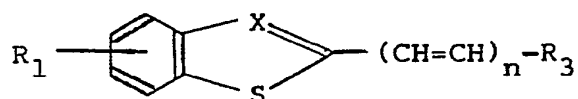
In an analogous manner as described in Example
2B, 5,6-dimethoxy-benzothiazole-2-carbonitrile was
15 converted to N-hydroxy-5,6-dimethoxy-benzothiazole-2-carboximidamide hydrochloride; m.p. 230-232 °C and then converted into its hydrochloride, m.p. 205-208 °C.

20

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CLAIMS

1. Benzothiazole and benzothiophene derivatives of the formula I

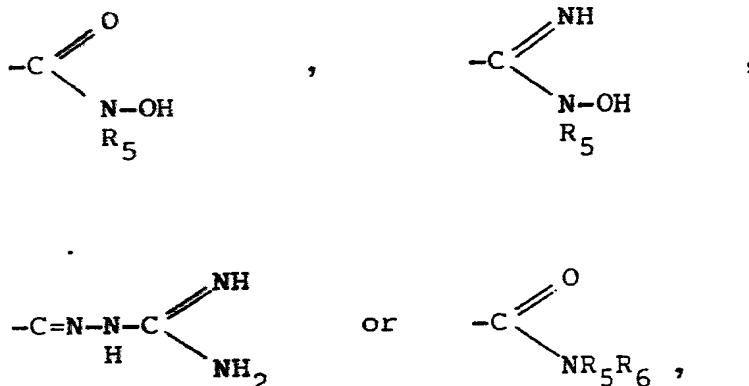


wherein

R_1 represents one up to and including four, the same or different substituents selected from alkyl(1-6 C), alkoxy(1-6 C), hydroxy, halogen, NO_2 , CF_3 or the group $-\text{NR}_5\text{R}_6$, whereby two substituents taken together may also represent a methylene dioxy group,

X represents nitrogen or the group $\overset{\text{R}_4}{\underset{|}{\text{C}}} =$,
 n has the value 0, 1 or 2,

R_3 represents one of the moieties:



the latter meaning of R_3 (amide) only under the condition that for X is nitrogen the meaning of R_1 is limited to substituents selected from hydroxy, alkoxy(1-6 C) and methylenedioxy, and R_4 , R_5 and R_6 represent hydrogen or alkyl(1-6 C) and pharmaceutically acceptable salts thereof.

2. Compound according to claim 1, in which X represents a $-\text{CH}=$ moiety.
3. Compound according to claim 1, in which R_1 represents at least two oxygen bearing substituents selected from alkoxy and hydroxy or in which R_1 represents a methylene dioxy group.
4. Compound according to claim 3, in which R_1 represents a dimethoxy or a hydroxy-methoxy substitution pattern.
5. Pharmaceutical preparation containing a compound according to claim 1 as the active principle in admixture with a pharmaceutically acceptable carrier.

6. Process of analogy for the preparation of a compound of formula I or a salt thereof characterized in that

- (a) a compound of formula II, wherein R_1 , n and X have the aforesaid meanings, or an acid halide or anhydride thereof is reacted with a compound of the formula III or V, wherein R_5 and R_6 have the aforesaid meaning or with a reactive derivative thereof, in which the hydrogen atom (at the nitrogen) has been replaced by a more reactive moiety, such as an alkali metal;
- (b) a compound of formula II or an acid halide or anhydride thereof is reacted with an alkali metal azide, followed by reduction of the resulting azide;
- (c) a compound of the general formula IV in which R_1 , X and n have the meanings assigned above is reacted with a compound of formula V, in which R_5 has the aforesaid meanings, or with a reactive derivative thereof, in which hydrogen (at the nitrogen) has been replaced by a more reactive moiety, such as an alkali metal;
- (d) a compound of the general formula VI, in which R_1 , X and n , is reacted with amino-guanidine or a salt thereof;

after which the compound thus prepared through (a), (b), (c) or (d),

in which R_1 is at least one alkoxy group may be hydrolysed into the corresponding compound, in which R_1 is at least one hydroxy group,

or the compound thus prepared in which R_1 is at least one hydroxy group may be alkylated into the corresponding compound in which R_1 is at least one alkoxy group

or the compound thus obtained in which R_1 represents at least two hydroxy groups may be converted into the corresponding compound in which R_1 represents at least a methylene dioxy group,

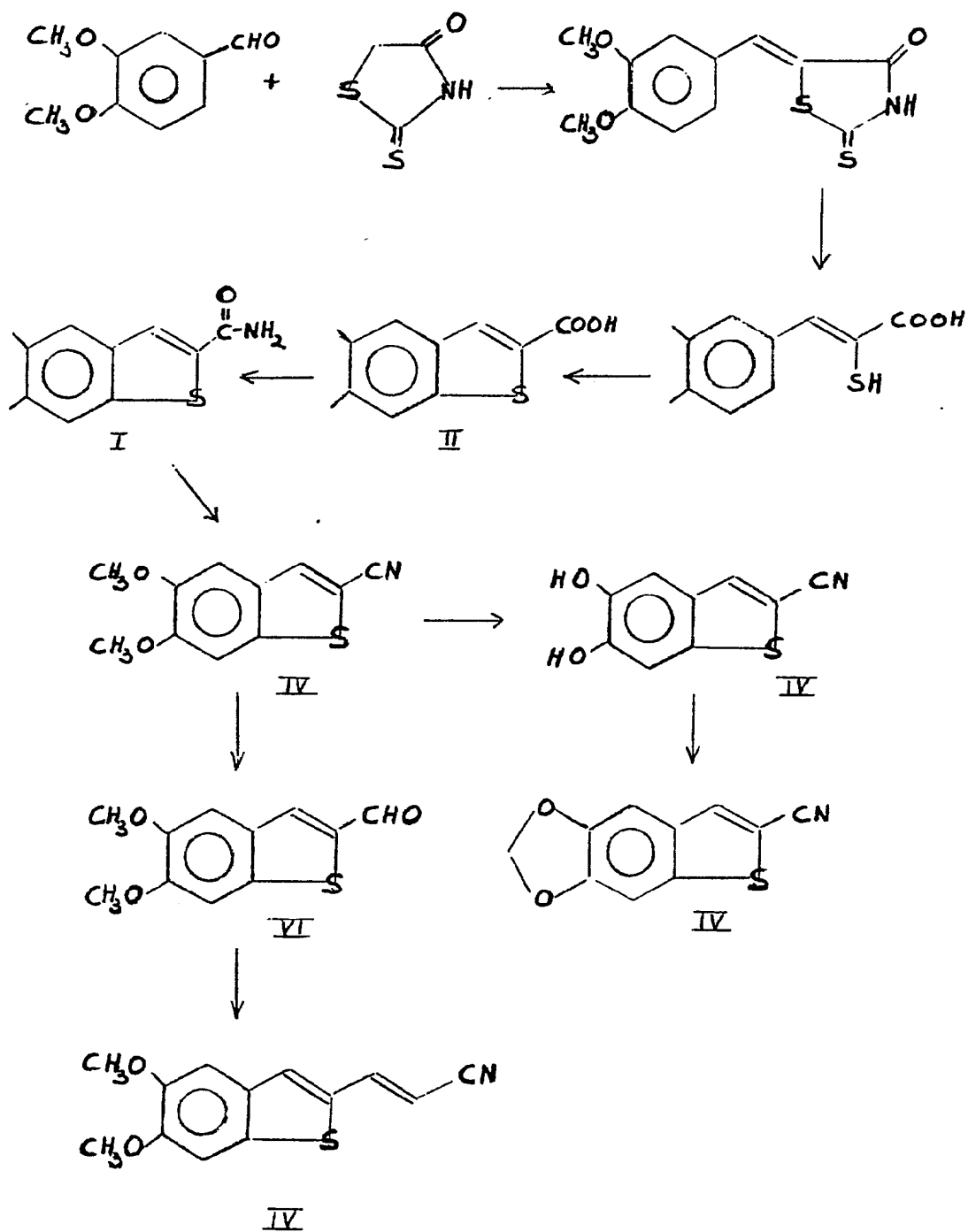
or the compound thus obtained in which R_1 represents at least one nitro group may be converted into the corresponding compound in which R_1 represents at least one amino group,

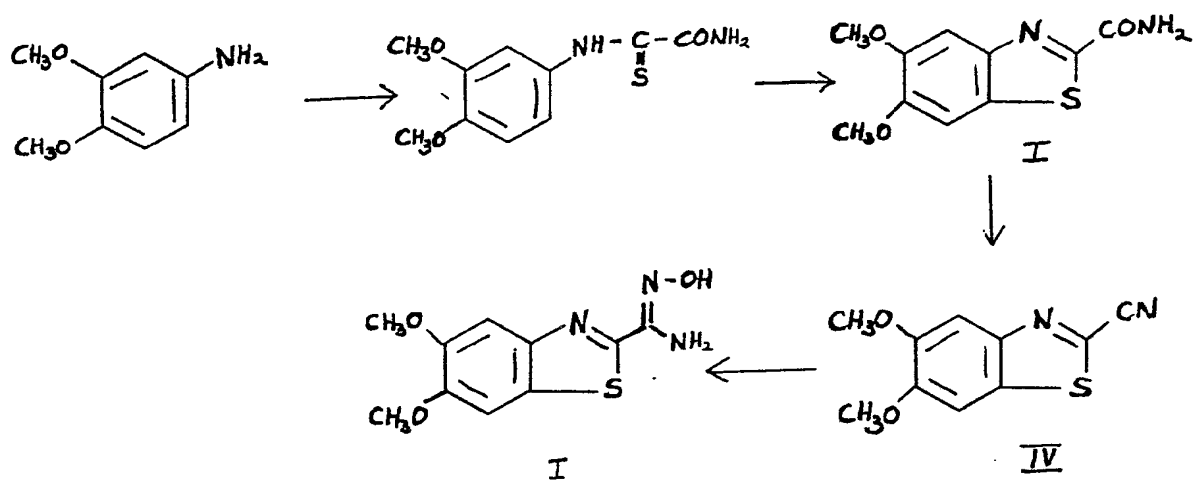
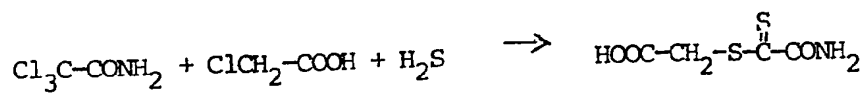
after which the resulting compound may be converted into a pharmaceutically acceptable salt.

7. The compound according to claim 1: N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide and pharmaceutically acceptable salts thereof.
8. The compound according to claim 1: 4-chloro-N-hydroxy-5,6-dimethoxy-benzo[b]thiophene-2-carboximidamide and pharmaceutically acceptable salts thereof.
9. The compound according to claim 1: 5,6-dimethoxy-benzo[b]thiophene-2-carboxamide.

FLOW CHART FOR BENZOTHIOPHENES

(e.g. starting products with X = -C=)







European Patent
Office

EUROPEAN SEARCH REPORT

01 58380

Application number

EP 85 20 0325

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
Y	DE-A-1 813 836 (ASPRO-NICHOLAS) * Claims *	1-6	C 07 D 333/70 C 07 D 277/68 C 07 D 333/60 C 07 D 333/58 C 07 D 495/04
Y	--- CHEMISCHE BERICHTE, vol. 106, no. 2, 1973, pages 639-654, Verlag Chemie GmbH, Weinheim, DE; F. BOHLMANN et al.: "Über ein neues Isoeugenol-Derivat aus Lepidophorum grisleyi Samp" * Page 640, introduction; pages 643-644 *	1,6	A 61 K 31/38 A 61 K 31/425// C 07 D 333/56
A	--- US-A-2 775 593 (R. BEHNISCH) * Column 3, example 3 *	1,2,6	
A	--- FR-A-2 207 725 (WARNER-LAMBERT) * Claims *	1-6	

			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 333/00 C 07 D 277/00 A 61 K 31/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 20-06-1985	Examiner CHOULY J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	